Preformulation factors and essential requirements:

- **Melting point:** It is the Temperature at which the solid and liquid phases are in equilibrium. Its determination is a primary indication of purity.
- **Solubility:** This property is essential for developing solution to be injected either intraveneously or intramuscularly. It is a function of chemical structure: salts of acid or bases are the drugs that can achieve the desired degree of water solubility.
- **Molecular structure and weight:** These are the basic characteristics of the drug from which the potential properties and reactivities of functional groups can be determined.
- **Particle Size and Shape:** Study of particle size give information about Solubility, dissolution rate and absorption etc.These charcterstics are determined by Scanning electron microscope or an optical microscope with polarizing attachments.
- **Ionisation constant:** This property is used to determine the PH-dependent solubility of a compound.Potentiometric PH titration or PH-solubility analysis is used for determining the PKa value.Ionisation constant of a compound also helps in determining the degree of ionization of an acid or base. Degree of ionization depends upon the PH.

For acidic drugs Pka ranges from 3-7.5 and for basic drugs Pka ranges from 7- 11.

- **Partition Coefficient (P):** It is a ratio of equilibrium concentration of drug in aqueous and oily phases in contact with each other at a constant temperature. Partition coefficient can be expressed as : P = [Coil / Cwater]],where, Coil= organic phase concentration and Cwater = aqueous phase concentration.
- **Hygroscopicity:** The tendency of a solid to take up water from atmosphere, as it is subjected to a controlled RH programe under isothermal condition. A high degree of hygroscopicity can adversely affect the physical and chemical properties of a drug substance.

Essential requirements for Formulation:

- In the preparation of parental products, the following substances are added to make a stable preparation.

1. Vehicles

2. Additives

a) Solubilizing agents b) Stabilizers c)Buffering agents d) Antibacterial agents e) Chelating agents f)Suspending ,emulsifying and wetting agents g)Tonicity factors

Vehicles

- There are two types of vehicles, which are commonly used for the preparation of injections

A) Aqueous vehicle - water is used as vehicle for majority of injections because water is tolerated well by the body and is safest to administer. The aqueous vehicle used are ;-

1) Water for injections.

2) Water for injection free from CO2 (carbon dioxide)

3) Water for injection free from dissolved air, water for injection is sterile water, which is free from volatile, non- volatile impurities and from pyrogens.

- Water for injection, contaminated with pyrogens may cause rise in body temperature if injected. Hence, test for pyrogen is done to ensure that water for injection is free from pyrogens.

B) Non -aqueous vehicles:-The commonly used non-aqueous vehicles are oils and alcohols. Fixed oil, such as arachis oil,cottonseed oil ,almond oil and sesame oil are used as vehicle. the oily vehicles are generally used when a depot effect of drug is required or the medicaments are insoluble or slightly soluble in water or the drug is soluble in oil example dimercaprol injection by using arachis oil as vehicle.

- Ethyl alcohol is used in the preparation of hydrocortisone injection .hydrocortisone is insoluble in water, hence the solution is made in 50% alcohol .Alcohol causes pain and tissue damage at the site of injection. Therefore, it is not used commonly.
- Propylene glycol is used as a vehicle in the preparation of digoxin injection .it is relatively nontoxic but it causes pain on S/C or I/M injection.

Additives

- These substances are added to increase the stability or quality of the product .These additives should be used only when it is necessary to use them. While selecting the additives, care must be taken that they should be compatible both physical and chemical with the entire formulation. They should be added in minimum possible quantity.

a) Solubilising agents:- These are used to increase the solubility of drugs which are slightly soluble in water .the solubility of drug is increased by using surface active agent like tweens and polysorbate or by using co solvents.

b) Stabilizers:- The drugs in the form of solution are more liable to deteriorate due to oxidation and hydrolysis .The stabilizers are added in the formulation to prevent this .the oxidation can be prevented by adding a suitable antioxidant such as, thiourea,ascorbic acid ,sodium metabisulphite, or the product is sealed in an atmosphere of Nitrogen or Carbon dioxide. hydrolysis can be prevented by using a non-aqueous vehicle or by adjusting the pH of the preparation.

- **Antioxidants:**
- Water soluble: Sulfurous acid salts, Ascorbic acid isomers, Thiol derivatives
- Oil soluble: Propyl gallate ,Butylated hydroxyanisole ,Ascorbyl palmitate, alpha Tocopherol

c) Buffering agents: -The degradation of the preparation, which is due to change in pH, can be prevented by adding a suitable buffer to maintain the desired PH .

pH	Buffer system	Concentration (%)
3.5-5.7	Acetic acid-acetate	1-2
2.5-6.0	Citric acid- citrate	1-5
6.0-8.2	Phosphoric acid- phosphate	0.8-2
8.2-10.2	Glutamic acid- glutamate	1-2

d) Antibacterial agents:- These substance are added in adequate quantity to prevent the growth of microorganism during storage. so these substances act as preservatives, antibacterial agents are added in single dose containers, where parenteral products are sterilized by filtration method and in multi dose containers to prevent microbial contamination .

Some typical preservative used in parenteral suspensions and their commonly used concentrations are as follows.-

- Benzyl alcohol (0.9% to 1.5%)
- Methylparaben (0.18% to 0.2%)
- Propylparaben (0.02%)
- Benzalkonium chloride (0.01% to 0.02%)
- Thiomersal (0.001% to 0.01%)

f) Chelating agent: - Chelating agents such as EDTA (Ethylene diamine Tetra acetic acid) and its salts, sodium or pottasium salts of citric acid are added in the formulation,to chelate the metallic ions present in the formulation. They form a Complex which gets dissolved in the solvent.

S. No.	Additives	Concentration range (%)
1	EDTA disodium	0.00368-0.05
2	EDTA calcium disodium	0.04
3	EDTAtetrasodium	0.01

g) Suspending, emulsifying and wetting agents:- The suspending agents are used to improve the viscosity and to suspend the particles for a long time. Methyl cellulose, carboxy-methyl cellulose, gelatin and acacia are commonly used as suspending agents .Emulsifying agents are used in sterile emulsions .for this purpose lecithin is generally used. The wetting agents are used to reduce the interfacial tension between the solid particles and the liquid, so as to prevent the formulation of lumps. They also act as antifoaming agents to subside the foam produced during shaking of the preparation.

Additives	Concentration range (%)
Polyethylene glycol 300	0.01-50.0
Polysorbate 20	0.01
Polysorbate 40	0.05
Polysorbate 80	0.04-4.0
Povidone	0.2-1.0
Propylene glycol	0.2-50.0
Sorbitan monopalminate	0.05
Dimethylacetamide	0.01
Lecithin	0.5-2.3

h) Tonicity factors: - Parenteral preparation should be isotonic with blood plasma or other body fluids. The isotonicity of the solution may be adjusted by adding sodium chloride, dextrose and boric acid etc. in suitable quantities. These substances should be compatible with other ingredients of the formulation. Examples of Tonicity adjuster/modifier are Glycerin, lactose, mannitol, dextrose, NaCl, sodium sulfate and sorbitol

Importance of Isotonicity

- An isotonic solution is one that exhibits the same effective osmotic pressure as blood serum.Isotonicity is important for parenteral preparation because if the solution is isotonic with blood, the possibility of product penetrating the RBC and causing haemolysis is reduced. For hypertonic solution crenation and for hypotonic solution haemolysis will occur.